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RESEARCH ARTICLE

Synthesis, Characterization and Biological Evaluation of Esters Derived from Sulfamethoxazole Drug

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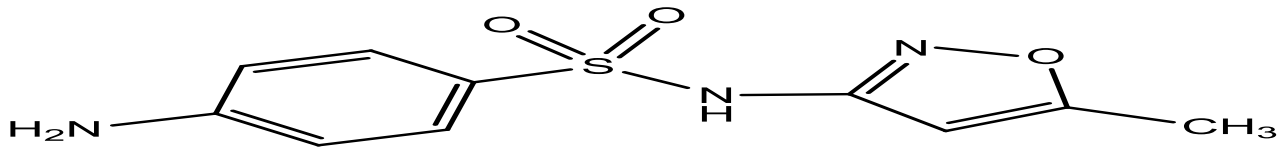
Abstract

A series of novel esters compounds have been prepared from the reaction of sulfamethoxazole drug with α-chloro acetyl chloride then reaction of the resulting compound with various carboxylic acids and carboxylic drugs. The modern ester has been diagnosed by ^{1}HNMR, FTIR spectral data and their physical properties and some of them were screened for their antibacterial activity.

Keywords: *Sulfamethoxazole, Esters, Antibacterial activity.*

Introduction

Sulfamethoxazole is a 4-amino-N-(5-methylisoxazol-3-yl) benzene sulfonamide, the molecular formula for it ($C_{11}H_{12}N_3O_3S$) (SMX) and has structure as shown below [1]:



It is in the type of sulfonamide that are widely utilized as antibacterial substance, because they overlap with *p*-amino benzoic acid (PABA)in the biosynthesis of tetrahydrofolic acid which is important for bacteria-Monti in the metabolic operation [2].A creation of hydrofolic acid is necessary for bacteria in order to survive [3,4]. Mixture of sulfamethoxazole and trimethoprim (SMX/TMP) which is known as co-trimoxazole is utilized to treat a broad variety of bacterial infection e.g.: (genitourinary tract infections), (middle ear infections), (respiratory-tract infections such as bronchitis and enteric infections).

The combination is also used to prevent and treat a certain type of pneumonia (pneumocystis-type) [5, 6]. As with any other drug there are some side effects maybe appear when use (SMX/TMP) such as: gastrointestinal upset and rash [7]. SMX work as (acid and base).as base because of presence the primary amine having pKa (1.39) and being acidic because of presence the secondary amine with pKa (5.81) [8]. Accordingly, we wish to report herein the synthesis of new esters with diverse heterocyclic ring and investigate its biological significance.

Experimental

Instruments

Melting points were registered by using {Stuart Melting Point apparatus}. Infrared spectra FTIR {Shimadzu -8300 Spectrophotometer} in Ibn Sina State Company (ISSC).^{1}HNMR spectra were written down on {Bruker-400 MHz} with used (TMS) as interior standard in DMSO-d6 as a solvent in AL- albayt University-Jordon.

Methods

Synthesis of {2-chloro-N-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl) acetamide} (C_1) [9]

Put in a suitable round a mixture of (0.016 mole) sulfamethoxazole drug and (10ml) DMF with (0.025mole) triethyl amine then added (0.016 mole) chloro acetyl chloride drop-wise in 5-10°C and stirred for (6 hr). The resulting solid filtered, dried then recrystallized by ethanol.

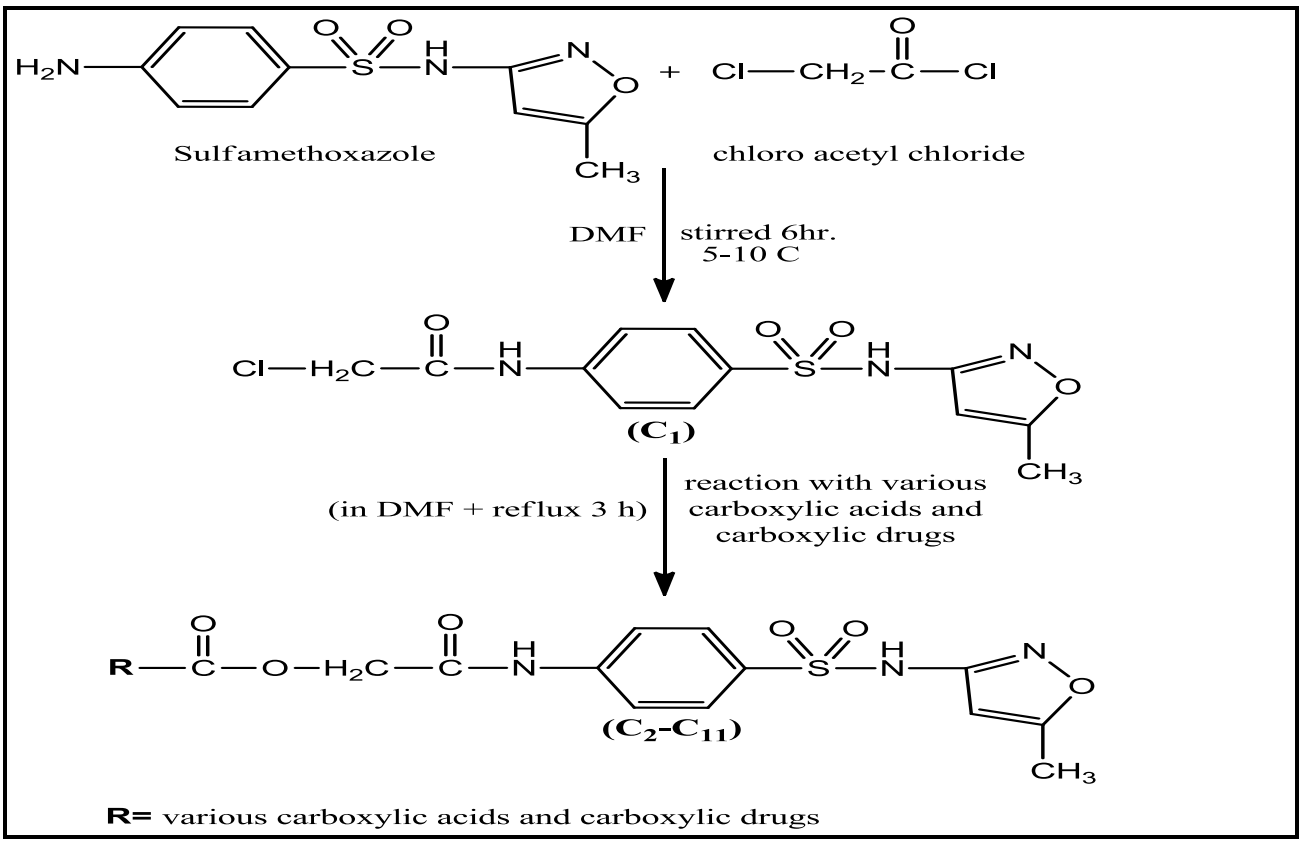
General Method for Synthesis of Esters by the Reaction of Compound (1) with Carboxylic Acids and Carboxylic Drugs (C_2-C_{11}) [10]

A mixture from (0.01mole) compound (1) and (0.01 mole) carboxylic acid (*p*-nitro benzoic acid, *m*-nitro cinnamic acid, *p*-chloro benzoic acid, benzoic acid, 3,5-dinitro benzoic acid) mixed with (0.011 mole) sodium iodide and (0.011mole) trimethylamine in (10 ml)DMF has been refluxed at 90°C for 3hrs.The resulted precipitate has been filtered and dried. The same method has been repeated with carboxylic drugs (Naproxen, Ibuprofen, Ciprofloxacin, Mefenamic acid, Ampiciline). Physical properties for a new compound listed in Table (1).

Antibacterial Activity Test [11]

A cup plate process using nutrient agar medium was used in examine the antibacterial activity for some prepared compounds against two type of bacteria, Staphylococcus aureus(gram+ ve) & Escherichia coli(gram-ve) respectively and DMSO has been used as a sample solution.

A sterilized cork borer cups was used and has been scooped in a petri dish out of agar medium which has been formerly vaccinated with microorganisms, the verified compound solution(0.1ml) has been poured in the cups then the petri dishes has been afterward brood at(37°C) for 48hrs. Zones of inhibition have been calculated in (mm), the results registered in Table (4).



Scheme 1: Synthetic route for new esters

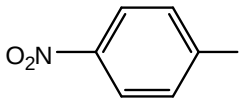
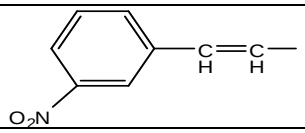
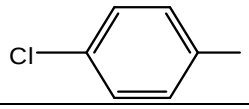
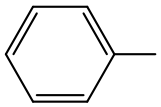
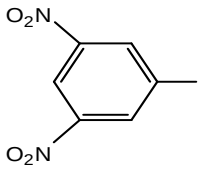
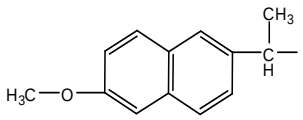
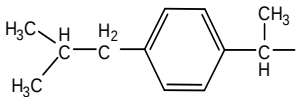
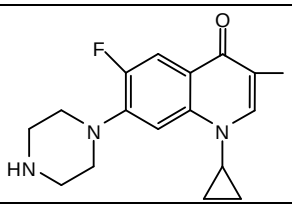
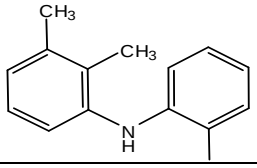
Results and Discussion

Esters can be prepared by refluxing compound (1) with carboxylic acids and drugs, Scheme(1).In general the new derivatives was characterized by physical properties, spectroscopic data, Tables (1),(2),(3). The FTIR spectrum of compound (4), Figure (9) shows bands at: (1681) cm^{-1} back to υ(C=O) ester,(1161,1319)$cm^{-1}$for υ(SO_2)and at(3444)cm^{-1}, (763)$cm^{-1}$for υ(NH) and υ(C-Cl) respectively. Compound (6), Figure (10) shows in addition to the above absorption bands a stretching band at (1346-1543) cm^{-1} due to υ (NO_2) group. Figure (11) showed FTIR spectrum of compound (7).

FTIR spectrum of compound (9), Figure (12) shows absorption brigades at: (1732), (877) cm^{-1} owned to υ(C=O) ester, υ(C-F) respectively.

^{1}HNMR spectral data of ester (3), Figure(13) exhibit signs at (δ ppm): (2.2) due to (CH) imidazole ring, (2.4) due to (CH_3)imidazole ring ,(2.9) due to (CH_2) Neighboring carboxyl group, (3.1) due to (CH=CH), (5.8)due to (NH) near sulfoxide group, (6.1) due to (NH)amide and multiple signals at (6.5-8.5) due to aromatic rings protons. ^{1}HNMR spectrum of compound (4), Figure (14) showed diagnostic signals at (δppm): (2.1) due to (CH_2), (2.4) due to (CH_3), (6.5) due to (NH) amide and the protons of aromatic rings appeared at (6.8-8.4). Figure (15) showed the ^{1}HNMR spectrum of compound (7), these signals and others has been registered in Table (3).

Table 1: Physical properties for prepared compounds (1-11)

Comp. No.	Molecular Formula M.wt.(gm/mol)	Nomenclature	-R	Yield %	Color	M.P°C
1	**$C_{12}H_{12}ClN_3O_4S$** 329.76	2-chloro-N-(4-(N-(5-methylisoxazol-3-yl) sulfamoyl)phenyl)acetamide	-	78	Biege	
2	**$C_{19}H_{16}N_4O_8S$** 460.42	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl amino)-2-oxoethyl-4-nitrobenzene		62	Light brown	Oily
3	**$C_{21}H_{18}N_4O_8S$** 486.45	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl amino)-2-oxoethyl-3-(3-nitrophenyl) acrylate		65	Dark brown	Oily
4	**$C_{19}H_{16}ClN_3O_6S$** 449.86	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl amino)-2-oxoethyl-4-chlorobenzoate		74	Dark brown	Oily
5	**$C_{19}H_{17}N_3O_6S$** 415.42	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl amino)-2-oxoethyl benzoate		77	Reddishbrown	Oily
6	**$C_{19}H_{15}N_5O_{10}S$** 505.41	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenylamino)-2-oxoethyl-3,5-dinitrobenzoate		72	Reddishbrown	Oily
7	**$C_{26}H_{25}N_3O_7S$** 523.56	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenylamino)-2-oxoethyl-2-(6-methoxynaphthalin-2-yl) propanoate		85	Orange	114-116
8	**$C_{25}H_{29}N_3O_6S$** 499.58	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenylamino)-2-oxoethyl-2-(4-isobutyl phenyl)propanoate		81	Orange	119-120
9	**$C_{29}H_{29}FN_6O_7S$** 624.64	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenylamino)-2-oxoethyl-1-cyclopropyl-6-floro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate		73	White	180-182
10	**$C_{27}H_{26}N_4O_6S$** 534.58	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenylamino)-2-oxoethyl-2-(2,3-dimethyl phenylamino)benzoate		70	Orange	160-162

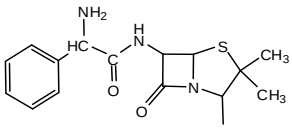
11	$C_{28}H_{30}N_6O_8S_2$ 642.70	2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenylamino)-2-oxoethyl-6-(2-amino-2-phenyl acetamido)-3,3-dimethyl-7-oxo-4-thia-1-aza bicyclo[3,2,0]heptan-2-carboxylate		69	Dark Orange	177-179

Table 2: FTIR spectral data cm^{-1} for all prepared compounds

Comp. No.	υ(C=O) cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}	υ(C-H)cm^{-1} aliphatic	υ(Ar-H) cm^{-1}	υ(C-N) cm^{-1}	υ(C-O) cm^{-1}	Other Band cm^{-1}
1	1681	1612	1500 1543	(2831-2985)	(3047-3170)	1495	1261 1334	υ(SO_2) 1165, 1396 υ(N-H) 3232, 3321
2	1701	1658	1508 1520	(2804-2993)	(3062-3120)	1462	1296 1307	υ(SO_2) 1165, 1346 υ(NO_2) 1369, 1527 υ(N-H) 3471
3	1701	1616	1597	(2873-2981)	(3016-3043)	1419	1280 1311	υ(SO_2) 1145, 1311 υ(NO_2) 1357, 1527 υ(N-H) 3451
4	1681	1616	1593	(2808-2978)	3051	1465	1373 1392	υ(SO_2) 1161, 1319 υ(N-H) 3444 υ(C-Cl) 763
5	1689	1616	1597	(2870-2981)	3051	1462	1377	υ(SO_2) 1157, 1319 υ(N-H) 3441
6	1701	1620	1597	(2873-2981)	3043 3093	1465	1265	υ(SO_2) 1161, 1323 υ(NO_2) 1346, 1543 υ(N-H) 3464
7	1728 1678	1620	1597	(2769-2974)	3143 3182	1469	1311	υ(SO_2) 1157, 1365 υ(N-H) 3468
8	1720	1620	1597	(2870-2954)	3140	1495	1369	υ(SO_2) 1161, 1319 υ(N-H) 3468
9	1732	1627	1508	(2870-2951)	3024	1485	1330	υ(SO_2) 1041, 1392 υ(N-H) 3990 υ(C-F) 887
10	1725	1620	1597	(2989-3007)	3143	1469	1315	υ(SO_2) 1157, 1369 υ(N-H) 3441
11	1740	1628	1590	(2870-2960)	3077	1460	1310	υ(SO_2) 1141, 1320 υ(N-H) 3400 υ(NH_2) 3450,3471

Table 3: ^{1}HNMR spectral information for esters (C_3, C4, C7)

Comp. No.	^{1}HNMR spectral information δ ppm
3	2.2(s,1H,CH imidazole ring); 2.4(s,3H,CH_3); 2.9(s,2H,CH_2); 3.1(d,2H, CH=CH ethylene group);5.8(s,1H,NH sulfoxide);6.1(s,1H,NH amide);(6.5-8.5)(m,8H,Ar-H)
4	2.1(s,2H,CH_2);2.4(s,3H,CH_3);(2.8-3.5)(m,1H,NH imidazole ring);6.1(s,1H,NH); 6.5 (s,1H,NH amide);(6.8-8.4)(m,8H,Ar-H)
7	1.4(s,1H,CH);2.4(s,3H,CH_3);2.9(s,2H,CH_2);3.4(s,3H,CH_3 imidazole ring);3.9(s,3H,O-CH_3); 6.1(s,1H,NH imidazole);6.5(s,1H,NH amide);(7.5-8.4)(m,8H,Ar-H)

Antibacterial Activity Study [12]

The biological activities have been determined by measuring the diameter around the well (Inhibition zone). From the data obtained it is clearly that compound (C_2) showed moderate to low activity against *Escherichia coli* and inactive against *Staphylococcus aureus*. Compounds (C_3), (C_4) and (C_7) possess moderate activity against *Staphylococcus aureus* in high concentration and inactive against *Escherichia coli*, while (C_8) showed moderate activity against both types of bacteria in high concentration only, and finally compound (C_9) showed highest activity against both types of bacteria at all concentrations. The results of antibacterial studies have been registered in Table (4).

Table 4: Antibacterial activity data of Sulfamethoxazole and prepared compounds

Comp. No.	Gram positive			Gram negative		
	Staphylococcus aureus			*Escherichia coli*		
	Conc. of extract gm/ml			Con. of extract gm/ml		
	0.1	0.01	0.001	0.1	0.001	0.001

SMX	20	18	15	20	15	14
C_2	-	-	-	11	9	9
C_3	10	-	-	-	-	-
C_4	12	-	-	-	-	-
C_7	12	8	-	-	-	-
C_8	14	11	-	15	-	-
C_9	34	34	34	35	35	35

Fig.1: Effect of (C_4) on *"Staphylococcus"*

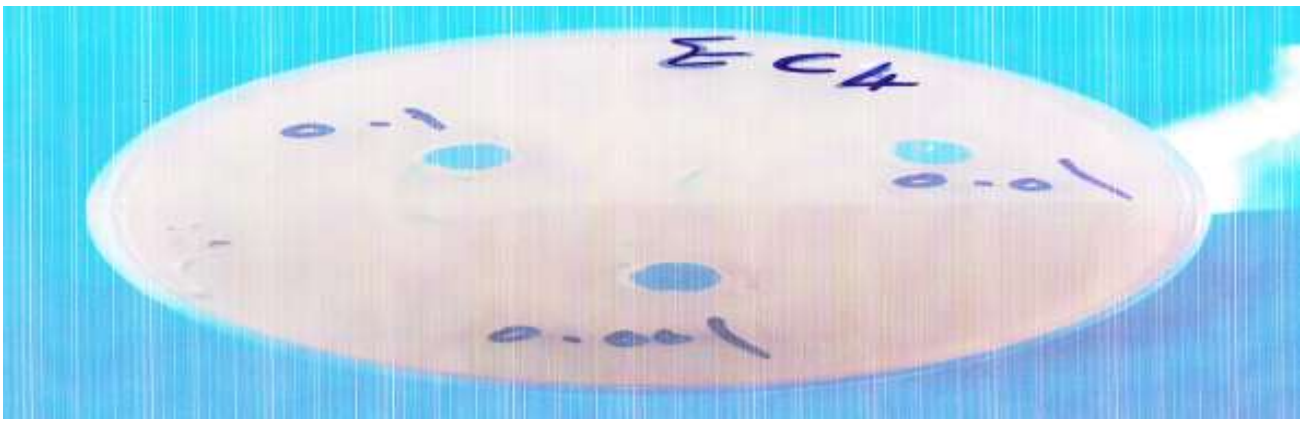


Fig.2: Effect of (C_4) on *"E.coli"*

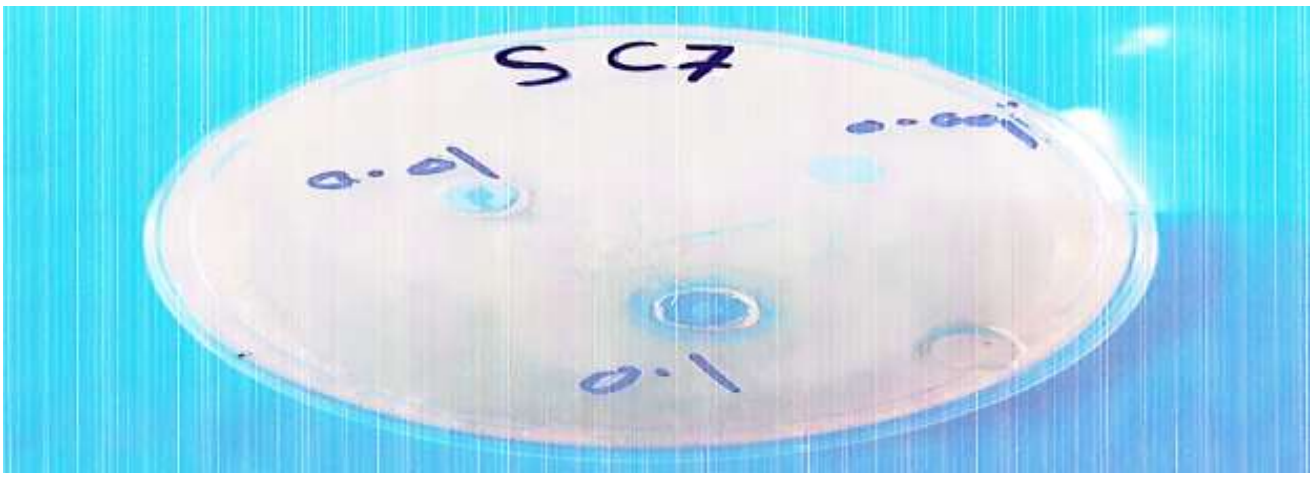


Fig.3: Effect of (C_7) on *"Staphylococcus"*

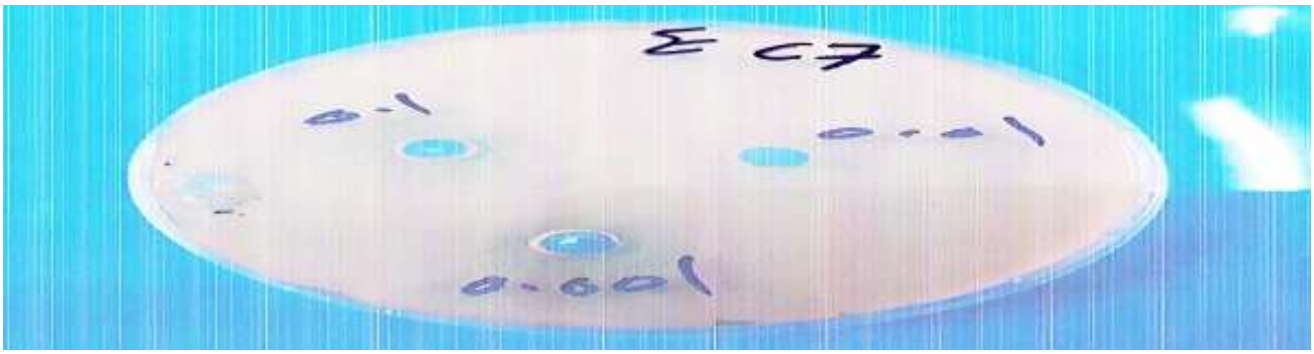


Fig.4: Effect of (C_7) on *"E.coli"*

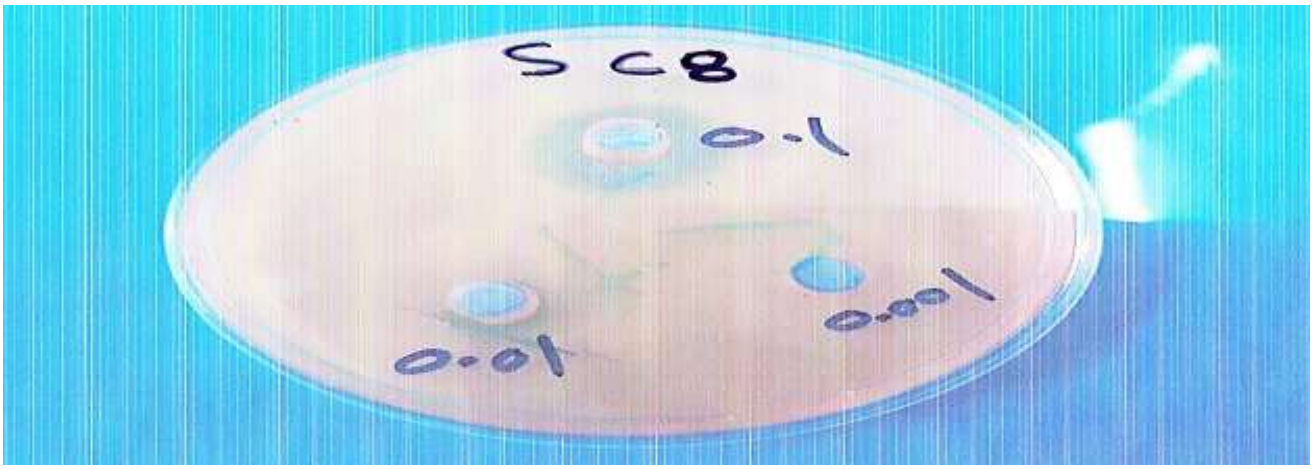


Fig.5: Effect of (C_8) on *"Staphylococcus"*

Fig6: Effect of (C_8) on *"E.coli"*

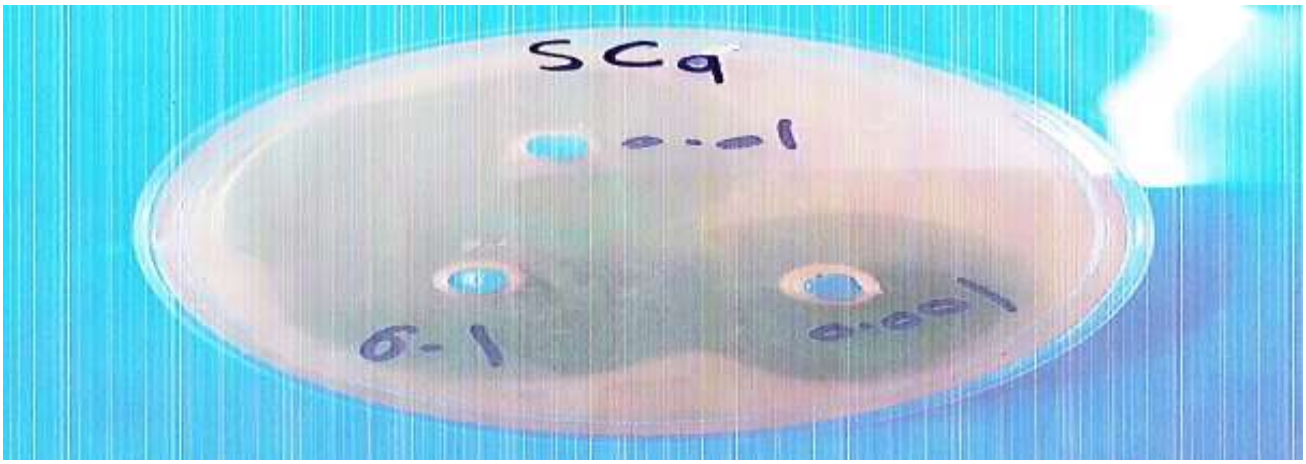


Fig.7: Effect of (C_9) on *"Staphylococcus"*

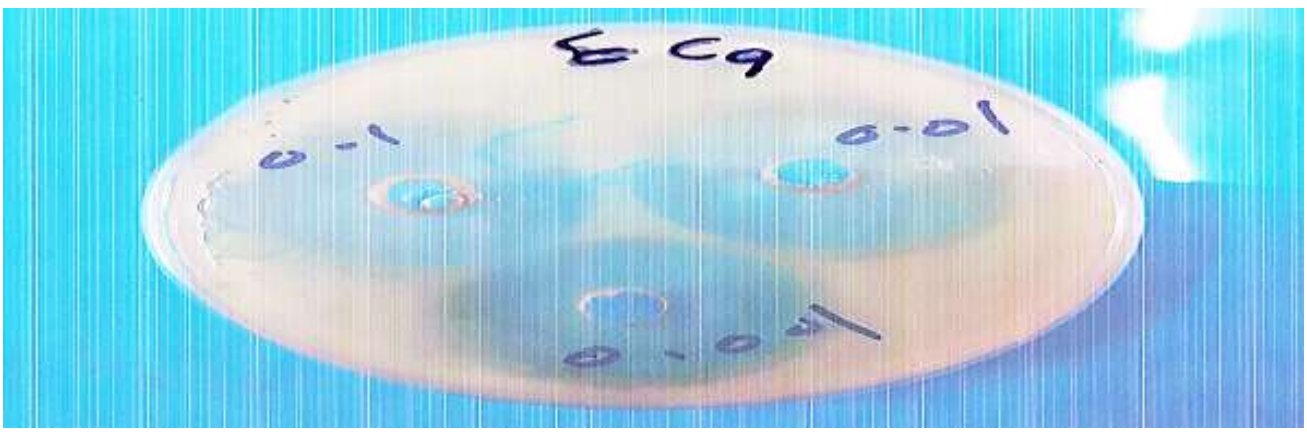


Fig. 8: Effect of (C_9) on *"E.coli"*

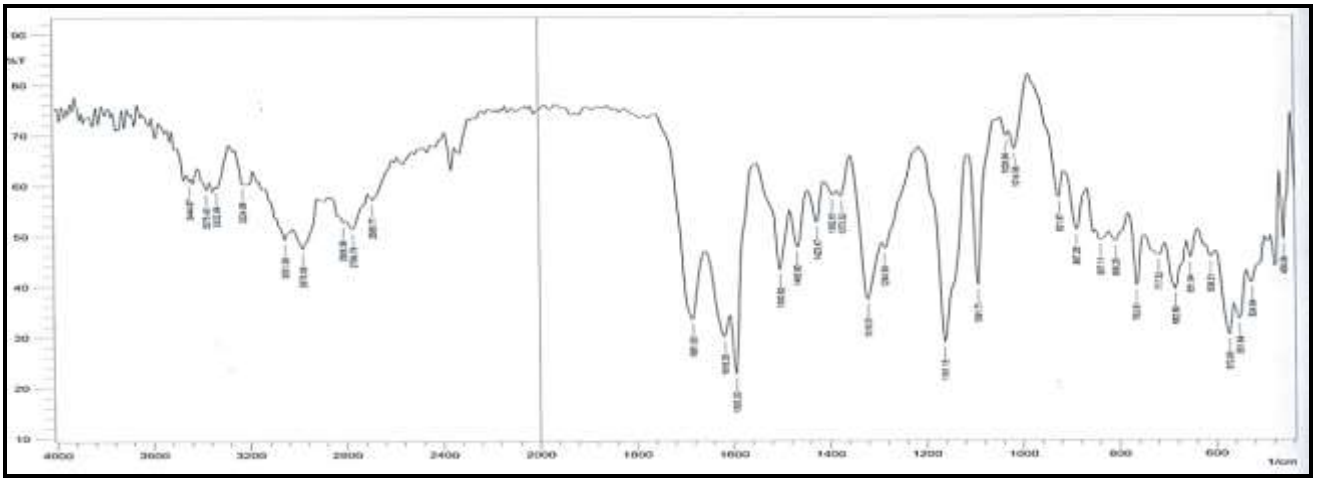


Figure 9: Spectrum of (C_4) by used FTIR

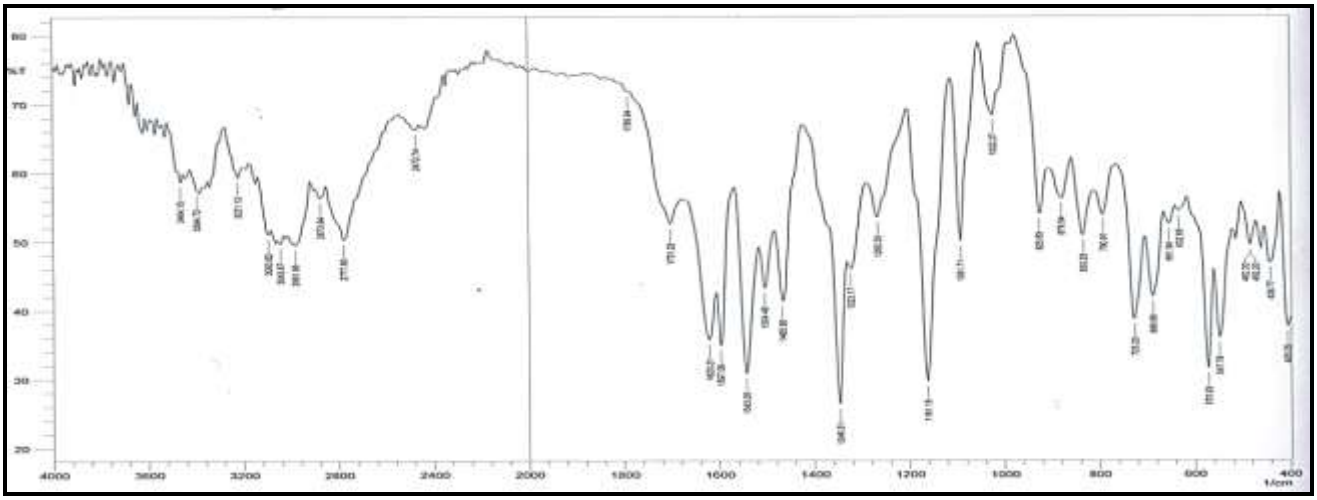


Figure 10: Spectrum of (C_6) by used FTIR

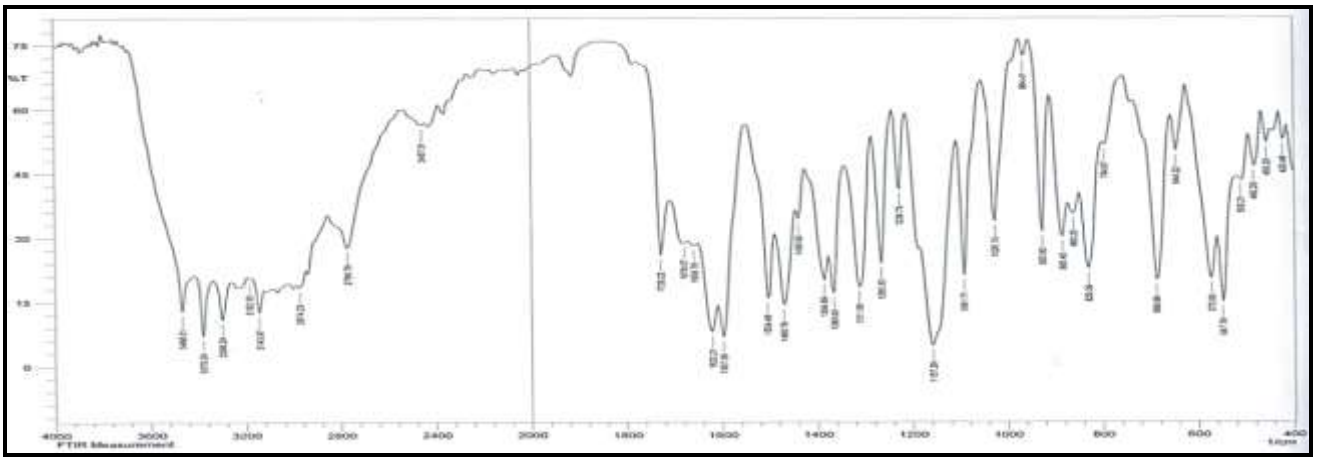


Figure 11: Spectrum of (C_7) by used FTIR

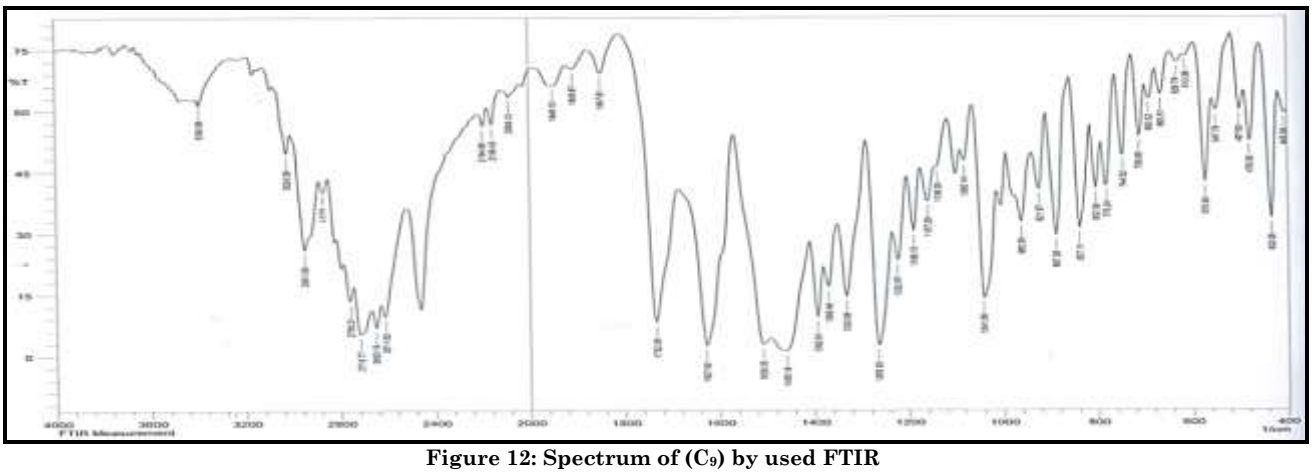


Figure 12: Spectrum of (C_9) by used FTIR

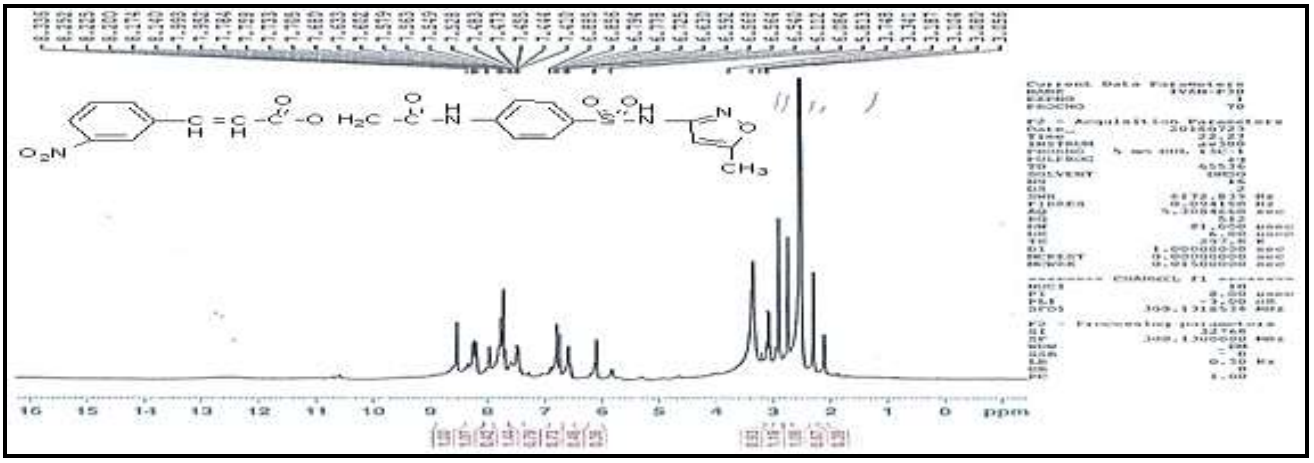


Figure 13: Spectrum of (C_3) by used ^{1}HNMR

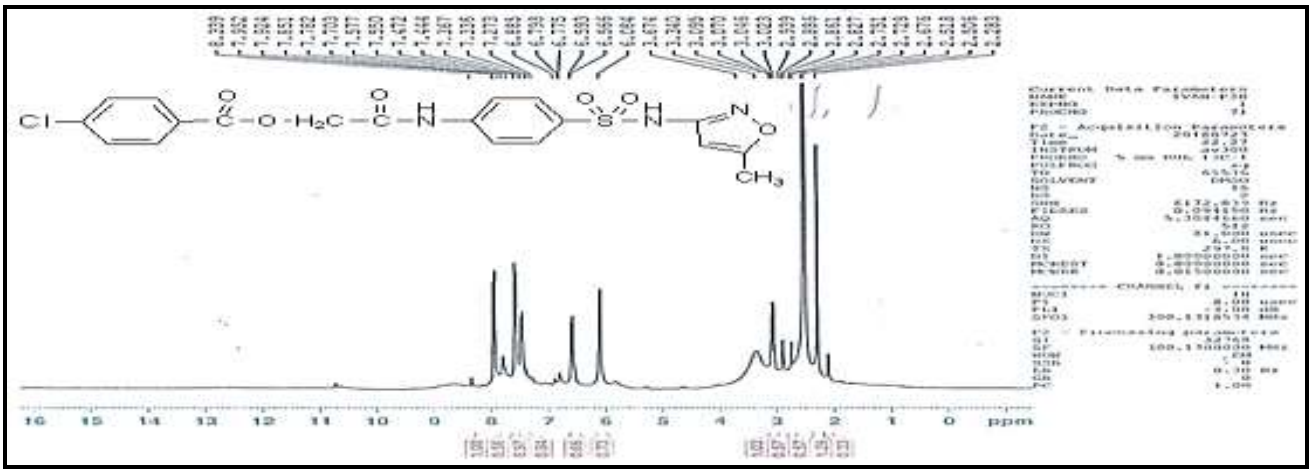


Figure 14: Spectrum of (C_4) by used ^{1}HNMR

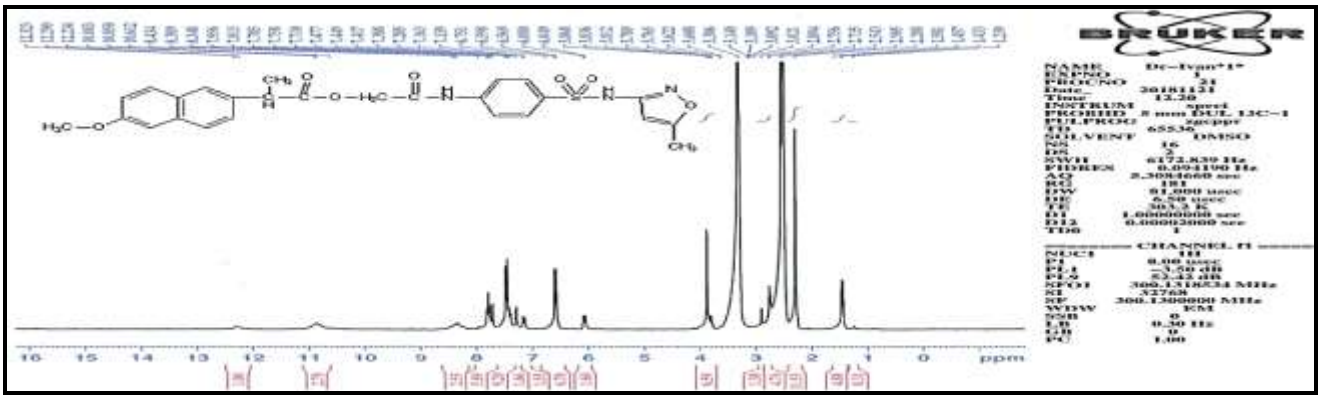


Figure 15: Spectrum of (C_7) by used ^{1}HNMR

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